

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Registry randomised trials: a methodologic perspective
AUTHORS	Doherty, Dorota; Tong, Steven; Reilly, Jennifer; Shrapnel, Jane; McDonald, Stephen; Ahern, Susannah; Harris, Ian; Tam, Charmaine S.; Brennan, Angela; Hodgson, Carol; Wilcox, Leonie; Balagurunathan, Anitha; Butcher, Belinda; Reid, Christopher

VERSION 1 – REVIEW

REVIEWER	Sparring, Vibeke Karolinska Institute
REVIEW RETURNED	08-Dec-2022

GENERAL COMMENTS	Really interesting and well-written paper on how registry randomised clinical trials can be embedded into large population-based registries or clinical registries. This is a smart, quick and cost-effective way of performing studies based on already collected data.
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REVIEWER	Lehtinen, Matti Tampereen Yliopisto, Faculty of Social Sciences
REVIEW RETURNED	26-Dec-2022

GENERAL COMMENTS	<p>Doherty et al. are to be commended for their attempt to review use of health registries as a basis for randomized trials. However, the scope is narrow with too much focus on the Australian situation. There is the important question on the population representativeness of clinical registries and underlying cohorts that is not really touched. The authors do not discuss quality of exposure assessment or (randomization of) interventions. Also lack or misclassification of the outcome information is not really considered, even if these can give rise to fundamental differences in which outcomes surface, when they surface and to what extent they are registered.</p> <p>Establishment of virtual registers is not described to satisfying extent and could be removed. On the contrary, in the end of the text use of registries to long term-follow up of randomized controlled trials is mentioned but should be expanded.</p>
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VERSION 1 – AUTHOR RESPONSE

Review 1:

We thank Dr Vibeke for the supportive comments on the manuscript. No specific comments were asked to be addressed

Reviewer 2:

We thank Dr Lehtinen for the important comments and respond as follows:

Comment 1: “the scope is narrow with too much focus on the Australian situation”.

Response: Unlike Sweden and a number of other countries around the world, clinical registries are in their infancy in Australia and the concept of undertaking a cost-effective approach to generating randomised evidence of comparative effectiveness is very new. This is the primary reason to focus on the Australian situation where we have the opportunity to support the development of capability and consideration of randomised registry trials in the development of the registry program.

To address the concern, we have included the following paragraphs in the manuscript outlining the international scope of randomised registry trials to broaden the focus of the manuscript and to provide the rationale for the focus on the Australian health care setting.

Unlike Australia, a number of countries have well established clinical registries and, for more than a decade, have developed the capability to undertake embedded randomised trials across a variety of clinical disciplines.¹⁻⁴ A well conducted scoping review identified 17 published trials using disease, procedure or health services registries.⁵ One of the early demonstrations of the RRCTs was the TASTE Trial undertaken in the SWEDEHEART clinical registry demonstrating no benefit of thrombus aspiration prior to percutaneous coronary intervention for improving clinical outcomes.⁶ Heralded as the “next disruptive technology” for undertaking randomised trials,⁷ the SwedeHeart registry has continued to perform a number of important comparative effectiveness trials and proposing international registry based randomised trials.

This review considers the benefits of RRCT, the types of questions they can answer, and some practical tips on how to successfully embed registry randomised trials in the Australian health care setting. It is based on a series of workshops held by the Australian Clinical Trials Alliance (ACTA) in May 2020. A glossary of terms used throughout is provided as Table 1.

Comment 2: There is the important question on the population representativeness of clinical registries and underlying cohorts that is not really touched

Response: We agree that the population representativeness is an important area and we have included the following paragraphs. We have also introduced a number of headings around trial considerations which these questions are addressing.

Trial Population Representativeness

An added benefit of RRCTs relate to the ability to address some of the concerns of the conventional RCTs, including the inadequate representativeness of trial populations.⁸ Embedding trials in clinical registries provides increased opportunity to systematically offer trial participation to “real-world patients” rather than opportunistically identifying potential trial participants. Studies comparing baseline characteristics of RCT trial populations with registry samples have identified lower risk profiles, with frequent exclusion of elderly patients and those with co-morbidities.⁹ Trial designs that recruit from real-world populations are likely to improve the external validity of the trial findings, providing physicians with appropriate evidence on which to base clinical decisions.¹⁰ However, the population coverage and representativeness of the clinical registry used for a RRCT also needs to be considered when generalising from such trials.

Comment 3: The authors do not discuss quality of exposure assessment or (randomization of) interventions

Response: We agree that the quality of exposure assessment or randomisation of interventions is important for high quality RRCTs. We have identified this area and included the following paragraphs.

Randomisation and Treatment Exposure Assessment in RRCTs

Randomisation can be readily achieved with web-based randomisation modules that can be linked to registry databases. Non-commercial, smartphone-accessible applications can enable rapid, accurate randomisation at the bedside making them highly suitable for adoption into registry-based trials.¹¹ Assuring adequate treatment exposure in RRCTs remains a similar challenge to conventional RCTs. Depending on the trial design, individuals or groups of patient's treatment allocation will be determined at the point of randomisation. In procedural registries, where the actual procedure to be undertaken varies, routine registry data collection should identify the procedural activity and highlight protocol deviations. In disease and health service registries, drug allocation, treatment compliance and persistence monitoring are required to ensure adequate treatment exposure – similar to conventional RCTs. The efficiency gain in RRCTs relies on the information being collected as part of routine registry follow-up data collection, but does not exclude other data being collected, such as data relevant to treatment compliance.

Comment 4: Also lack or misclassification of the outcome information is not really considered, even if these can give rise to fundamental differences in which outcomes surface, when they surface and to what extent they are registered.

Response: The issue of misclassification of outcome information is a very important topic and this has been discussed on pages 5 and 6. We have identified potential problems with using the current Australian classification systems as end-point measures due to mis-classification errors. We have recommended that for RRCTs, outcomes be clearly defined and potentially an endpoint adjudication committee be formed for the trial to ensure consistent and accurate outcomes ascertainment is achieved.

Comment 5: Establishment of virtual registers is not described to satisfying extent and could be removed.

Response: We have expanded the section to include some recommendations in regards to the suitability of electronic medical record systems for use in RRCTs. We feel it is important to keep this section in this paper as it is highlighted as a priority area for clinical quality registries in order to facilitate their use for research purposes in Australia. The following sentence has been added to this section.

The adoption of universal definitions of clinical events coded into EMRs would be an important development in the use of these systems for RRCTs.

Comment 6: On the contrary, in the end of the text use of registries to long term-follow up of randomized controlled trials is mentioned but should be expanded.

Response: We have agreed and have expanded this into a paragraph as follows.

A number of large scale clinical trials have utilised this method to report of longer term observational clinical outcomes following the shorter term observation of the clinical trials.¹²⁻¹⁴ This strategy is valuable for mandatory reporting registries, such as cancer and death registries and provides valuable information in relation to long terms outcomes following a particular intervention or treatment.

However, it has also proven valuable for trials of acute interventions and shorter term follow-up in COVID-19 treatment trials.¹⁵

We look forward to receiving further correspondence in relation to the manuscript.

Yours sincerely,

Christopher M Reid.

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